

U.S.S.N. 10/614,866

Filed: July 8, 2003

PRELIMINARY AMENDMENT

Amendment**In the Specification**

Please delete Figures 1A, 1B, and 1C from the specification.

Please amend the paragraph beginning on line 3, page 6 of the specification as follows.

Brief Description of the Drawing

~~Figure 1A is a structural schematic of zinc bis-oxycodone. Figure 1B is a structural schematic of zinc oxycodone stearate. Figure 1C is a structural schematic of zinc oxycodone distearate.~~

Please amend the paragraph beginning on line 4, page 13 of the specification as follows.

In yet another embodiment the lipophilicity of the drug is increased by forming a stable complex between a drug molecule (either charged or uncharged) and a metal cation such as zinc, magnesium, calcium, bismuth or the like. This complex may consist of one or more drug molecules, one or more metal cations, and, optionally, one or more lipophilic charged species. The aforementioned charged lipophilic species are incorporated into the complex if necessary to bring the charge of the final complex to zero and increase its overall lipophilicity. In general lipophilic acids or amines with chain lengths between C₅-C₃₀ are lipophilic counter-ion candidates. ~~Examples of such complexes for a narcotic drug oxycodone are given in Figure 1; a lipophilic drug complex may be composed of one or two oxycodone molecules, one Zn²⁺ cation, and one or two stearate anions. It is understood by one skilled in the art that various metal cations as well as lipophilic counter-ions can be used to form complexes with an analogous structure, for example, oxymorphone.~~

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Please amend the paragraph beginning on line 7, page 21 of the specification as follows.

In some embodiments, the immediate release portion of the dosage form comprises a lipophilic drug derivative. For example, salt derivatives or complexes that are insoluble at a neutral pH but dissociate, thereby releasing the parent compound, at an acidic pH are ideal for immediate release within the stomach. In the case of oxycodone some salts that may exhibit this property include, but are not limited to, the tannate, phthalate, salicylate, gallate, pectinate, phytate, saccharinate, asesulfamate and terephthalate salts. Complexes of drug with one or more metal ions and, optionally, one or more lipophilic counter-ions (~~see, for example, Figure 1~~) may also be used for immediate drug release. Use of salts or complexes in the immediate release portion of the dosage form reduces the abuse potential of the immediate release dose if the formulation is crushed and (1) snorted or (2) dissolved in water since these salts will be poorly soluble under these conditions. It is understood by the one of ordinary skill in the art that such salts or complexes may also be used to formulate an immediate release dosage form without a sustained release portion.

Please amend Example 1 of the specification as follows.

Example 1: Preparation of lipophilic oxycodone derivatives**A. Oxycodone free base**

The free base of oxycodone was prepared from its hydrochloride salt by the following method: Oxycodone hydrochloride was dissolved in water and sodium carbonate was added in the amount required to neutralize hydrochloric acid. Methylene chloride was added in order to extract the formed oxycodone free base. The obtained organic layer was dried over sodium

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sulfate and methylene chloride was evaporated using rotary evaporator. The obtained oxycodone free base was purified by crystallization.

~~B. Zinc bis-oxycodone~~

~~Zinc bis-oxycodone can be obtained in anhydrous media by reacting oxycodone free base with $\text{Zn}(\text{Et})_2$~~

~~C. Zinc oxycodone stearate~~

~~Zinc oxycodone stearate can be obtained in anhydrous media by reacting oxycodone free base with $\text{Zn}(\text{Et})(\text{C}_{18}\text{H}_{35}\text{O}_2)$~~

~~D. Zinc oxycodone di stearate~~

~~Zinc oxycodone di stearate can be obtained by co-melting $\text{Zn}(\text{C}_{18}\text{H}_{35}\text{O}_2)_2$ and oxycodone free base.~~

~~B B. Oxycodone Terephthalate~~

Oxycodone terephthalate is commercially available and can be used without further processing

The structures of some representative oxycodone zinc complexes are shown in Figures 1A, 1B and 1C.

Please amend Example 2 of the specification as follows.

Example 2: Preparation of Drug Containing Microparticles

The free base, or salts or complexes from Example 1 are added to molten hydrogenated vegetable oil, mixed, extruded and spheronized to form drug containing microparticles.